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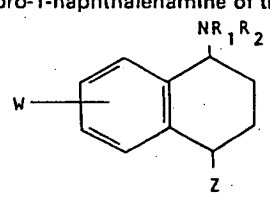
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(54) Antidepressant derivatives of trans-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine and pharmaceutical compositions thereof.

(57) Novel *trans*-isomeric derivatives of 4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine of the formula:



**EP 0 028 901 A1**

and the pharmaceutically acceptable acid addition salts thereof, wherein R<sub>1</sub> is hydrogen or normal alkyl of from 1 to 3 carbon atoms, R<sub>2</sub> is normal alkyl of from 1 to 3 carbon atoms, Z is phenyl substituted by X and Y where X and Y are each hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms or cyano, with at least one of X and Y being other than hydrogen, and W is hydrogen, fluoro, chloro, bromo, trifluoromethyl or alkoxy of from 1 to 3 carbon atoms; are useful as antidepressant agents. These novel compounds act to block the synaptosomal uptake of norepinephrine and serotonin (5-hydroxy-tryptamine), thereby alleviating abnormalities at central receptor sites.

P.C. (Ph) 6225A

ANTIDEPRESSANT DERIVATIVES OF TRANS-4-PHENYL-1,2,3,4-  
TETRAHYDRO-1-NAPHTHALENAMINE  
AND PHARMACEUTICAL COMPOSITIONS THEREOF

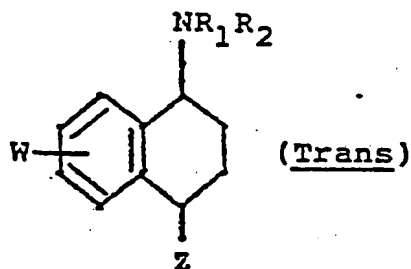
5 Serotonin and norepinephrine are known to be  
important chemical messengers participating in the  
transmission of nerve impulses in the brain. These  
messengers are liberated at specific sites on pre-  
synaptic cells and received, to complete transmission  
of the impulse, at specific sites on post-synaptic  
cells. Their effect is then terminated by metabolism  
10 or by uptake into the pre-synaptic cells. Drugs capable  
of blocking the pre-synaptosomal uptake of norepinephrine  
in the brain, thereby alleviating norepinephrine  
abnormalities at adjacent post-synaptic receptor sites,  
comprise a major category of antidepressant agents.  
15 It is also becoming a widely held view in the  
medicinal chemistry field that drugs capable of  
blocking the pre-synaptosomal uptake of serotonin in  
the brain will comprise another major category of  
antidepressant agents.

20 U.S. Patents 4,029,731 and 4,045,488 disclose a  
series of 4-phenyl-1,2,3,4-tetrahydro-naphthalen-1-  
amines and substituted amines useful as antidepressant  
agents. The preferred embodiment disclosed in these  
patents is the enantiomer trans-(1R)-N-methyl-4-phenyl-  
25 1,2,3,4-tetrahydro-1-naphthalenamine and its  
pharmaceutically acceptable acid addition salts.

We have now surprisingly discovered that certain  
novel trans-isomeric derivatives of 4-phenyl-1,2,3,4-  
tetrahydro-1-naphthalenamine are useful as antidepressant  
30 agents. The series of novel compounds of this invention

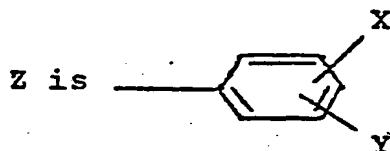
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consists of trans-isomeric bases of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

- 5  $R_1$  is selected from the group consisting of hydrogen and normal alkyl of from 1 to 3 carbon atoms,  $R_2$  is normal alkyl of from 1 to 3 carbon atoms,



- 10 X and Y are each selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms and cyano, with at least one of X and Y being other than hydrogen, and

- 15 W is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl and alkoxy of from 1 to 3 carbon atoms. The term "trans-isomeric" refers to the relative orientation of the  $NR_1R_2$  and Z moieties on the cyclohexene ring (i.e. they are oriented on opposite sides of the ring). Because both the 1- and 4- carbons of formula I are asymmetrically substituted, each trans- compound
- 20 has two optically active enantiomeric forms denoted (with reference to the 1-carbon) as the trans-(1R) and trans-(1S) enantiomers. The preferred embodiment is the enantiomer trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine and its

pharmaceutically acceptable acid addition salts.

The invention disclosed herein comprises the novel antidepressant compounds of formula I, the novel pharmaceutical compositions containing an amount  
5 effective in combatting mental depression of a compound of formula I as the essential active ingredient in a pharmaceutically acceptable carrier, and the novel method for combatting mental depression in a mentally-depressed subject which comprises administering to said  
10 subject an effective amount of a compound of formula I.

The compounds of this invention exhibit anti-depressant and anorectic activity in vivo in mammals, including human beings. At least a substantial portion of this activity results from their ability to block  
15 the synaptosomal uptake of either norepinephrine or serotonin (5-hydroxytryptamine), or both. The compounds of the invention possess negligible anticholinergic and monoamine oxidase inhibition activities.

By "pharmaceutically acceptable" acid addition  
20 salts is meant those salts which are non-toxic at the dosages administered. The pharmaceutically acceptable acid addition salts of the free bases of the invention are prepared by simply treating the free bases with various mineral and organic acids which form non-toxic  
25 acid addition salts, such as the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, maleate, fumarate, citrate, acid citrate, tartrate, bitartrate, succinate, gluconate and saccharate salts.

30 The preponderance of pharmaceutical activity of the trans-isomer compounds of formula I resides in the (1R)-enantiomeric forms thereof. Thus, one preferred

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group of the compounds of formula I consists of the (1R)-enantiomers and the racemic mixtures of (1R)- and (1S)-enantiomers of said compounds. This preferred group is referred to hereinafter as Group A.

5           One preferred group of the compounds of Group A consists of those wherein  $R_1$  is hydrogen or methyl,  $R_2$  is methyl and Z is selected from the group consisting of 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-bromophenyl and 4-bromophenyl. These compounds  
10       possess the highly desirable combination of excellent norepinephrine uptake blocking activity with excellent serotonin uptake blocking activity.

          Another preferred group of the compounds of Group A consists of those wherein  $R_1$  is methyl,  $R_2$  is methyl, W is hydrogen and Z is selected from the group  
15       consisting of 3-trifluoromethyl-phenyl and 4-trifluoromethyl-phenyl. These compounds exhibit synaptosomal uptake blocking activity that is highly selective for serotonin over norepinephrine. This is an important  
20       pharmacological property because, e.g., it is believed that the selective blockade of synaptosomal uptake of serotonin is beneficial in the treatment of certain types of mental depression. Recently, the  
antidepressant activity of two new drugs, zimelidine and  
25       fluvoxamine, has been attributed to their ability to selectively block the uptake of serotonin (compared to norepinephrine blockade).

          Particularly valuable are the following compounds, in either the (1R)-enantiomeric or (1S)(1R) racemic  
30       forms, and their pharmaceutically acceptable acid addition salts:

Trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N-methyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

5 Trans-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N,N-dimethyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

10 Trans-N,N-dimethyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N,N-dimethyl-4-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

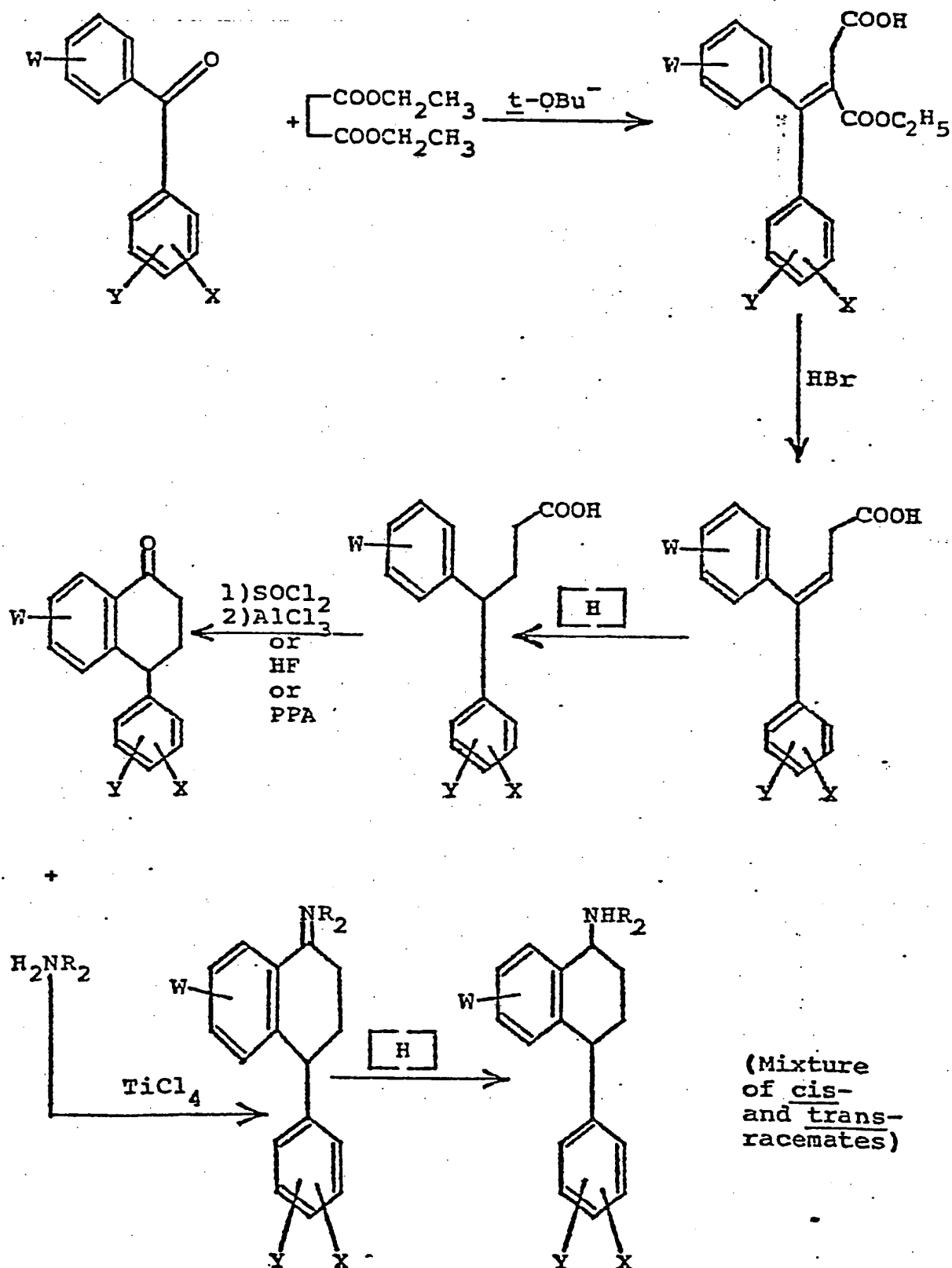
Trans-N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine; and

15 Trans-N-methyl-4-(4-chlorophenyl)-7-chloro-1,2,3,4-tetrahydro-1-naphthalenamine.

Of interest also is the (1S)-enantiomer of trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine, which exhibits surprisingly good  
20 norepinephrine and serotonin uptake blocking activity.

The compounds of the invention may be prepared by methods familiar to those skilled in the art. Those compounds wherein R<sub>1</sub> is hydrogen and neither X nor Y is alkoxy may be prepared from the appropriate substituted  
25 benzophenone starting material via the following reaction scheme:



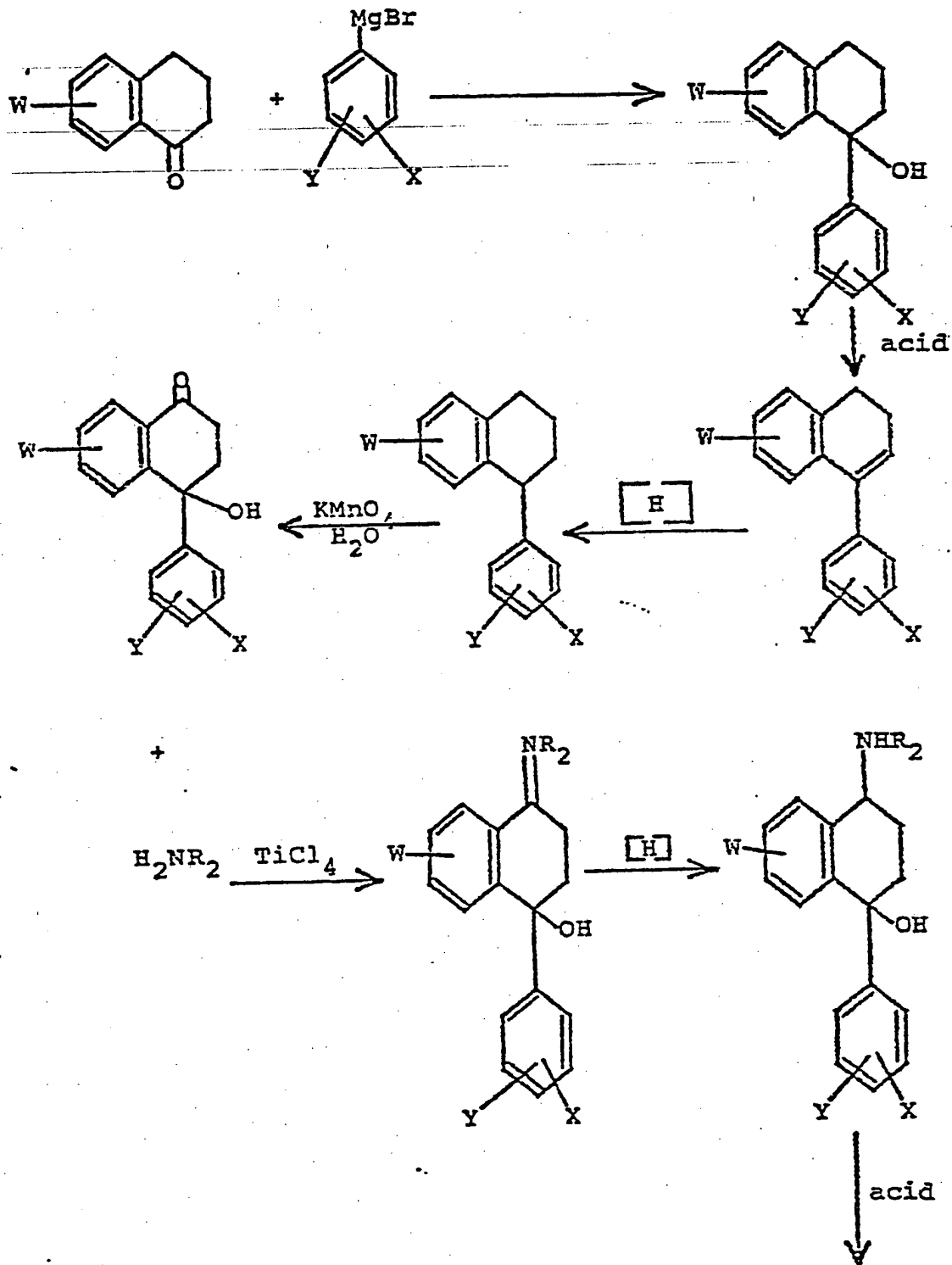


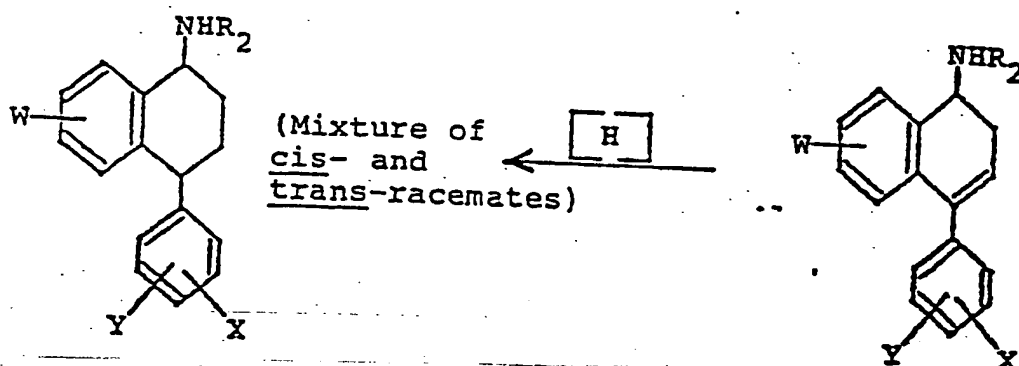
The first step in the above synthesis is a base-catalyzed Stobbe condensation of the substituted benzophenone with diethyl succinate. The next step is a hydrolysis and decarboxylation, e.g. with HBr. The resulting 4,4-  
5 diarylbut-3-enoic acid is reduced, e.g. with hydrogen over a catalyst or with HI and red phosphorus, to yield a 4,4-diarylbutanoic acid. The next step is a cyclization to yield a substituted tetralone, in the presence of, e.g., HF, polyphosphoric acid or thionyl chloride  
10 followed by  $\text{AlCl}_3$ . The substituted tetralone is condensed with the appropriate primary amine  $\text{H}_2\text{NR}_2$  in the presence of an acid catalyst, e.g.  $\text{TiCl}_4$ , to yield a 1-imine, which is then reduced to the 1-alkylamine (mixture of cis- and trans-racemates), e.g. by catalytic  
15 hydrogenation or with a metal hydride complex. The trans:cis ratio is generally increased by performing the final reduction step with zinc in the presence of acetic acid.

Those compounds wherein  $\text{R}_1$  is alkyl and neither  
20 X nor Y is alkoxy may also be prepared by the reaction scheme outlined above. The condensation of the substituted tetralone with the appropriate secondary amine  $\text{NHR}_1\text{R}_2$  in the presence of an acid catalyst, e.g.  $\text{TiCl}_4$ , yields a 3,4-dihydro-1-dialkylamine compound, which is  
25 then reduced to the 1,2,3,4-tetrahydro-1-dialkylamine (mixture of cis- and trans-racemates), e.g. with sodium borohydride in the presence of acetic acid.

Certain of the substituted benzophenone starting materials are commercially available, including 4-chloro-  
30 benzophenone, 4,4'-dichloro-benzophenone, 4-fluorobenzophenone and 4-bromobenzophenone. Those not commercially available may be prepared by various well known methods, such as the reaction of a substituted benzoyl chloride with benzene in the presence of  $\text{AlCl}_3$ , or the reaction  
35 of (optionally substituted)phenyl magnesium bromide with a substituted benzonitrile.

Those compounds wherein  $R_1$  is hydrogen, including those wherein either X or Y (or both) is alkoxy, may also be prepared from 1-tetralone or a substituted derivative thereof via the following reaction scheme:





The first step in the above synthesis is a reaction of the tetralone with an appropriate Grignard reagent, followed by hydrolysis. The resulting compound is dehydrated with acid, followed by hydrogenation to yield a 1-(substituted phenyl)-tetralin compound (optionally substituted by W). This compound is oxidized by potassium permanganate in the presence of water to yield a 4-hydroxy-1-tetralone derivative. This substituted tetralone is condensed with the appropriate primary amine  $H_2NR_2$  in the presence of an acid catalyst, e.g.  $TiCl_4$ , to yield a 1-imine, which is then reduced to a 1-alkylamine, e.g. with a metal hydride complex. The resulting 4-hydroxy-1-alkylamine is dehydrated with acid, and the dehydration product hydrogenated to yield the 1,2,3,4-tetrahydro-1-alkylamine compound (mixture of cis- and trans - racemates). In certain cases the second (dehydration) and third (hydrogenation) steps of the above synthesis can be omitted.

Those compounds wherein  $R_1$  is alkyl may also be prepared by the reaction scheme outlined immediately above. The condensation of the 4-hydroxy-1-tetralone derivative with the appropriate secondary amine  $HNR_1R_2$  in the presence of an acid catalyst, e.g.  $TiCl_4$ , yields a 3,4-dihydro-4-aryl-4-hydroxy-1-dialkylnaphthalenamine compound, which is then reduced to the 1,2,3,4-tetrahydro-4-aryl-4-hydroxy-1-dialkylnaphthalenamine, e.g. with sodium borohydride in the presence of acetic acid. The rest of the synthetic route is unchanged.

Certain of the optionally substituted tetralone starting materials are commercially available, including 1-tetralone. Those not commercially available may be prepared by synthesis methods well known to those skilled in the art.

The products of the synthetic methods described above are mixtures of cis- and trans-isomers. These isomers may be separated by methods known to those skilled in the art, e.g. fractional crystallization or chromatography.

Cis-isomeric compounds are described in more detail in our copending application, Serial No. 090,240, entitled "Antidepressant Derivatives of Cis-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine", filed November 1, 1979.

Resolution of the racemic trans-isomeric compounds of this invention into the (1R)- and (1S)-enantiomers is achieved by treating a solution of the trans-racemate free base with an optically active selective precipitant acid such as D-(-)-mandelic acid, L-(+)-mandelic acid, (+)-10-camphorsulfonic acid or (-)-10-camphorsulfonic acid, whereby the less soluble diastereomeric salt form is subsequently isolated as a crystalline precipitate.

Acid addition salts of the free bases of formula I (in either the racemic or optically active form) may be prepared by conventional procedures such as by mixing the amine base in a suitable solvent with the appropriate acid and recovering the salt by evaporation or by precipitation upon adding a non-solvent for the salt. Hydrochloride salts may readily be prepared by passing hydrogen chloride through a solution of the amine base in an organic solvent.

The activity of the compounds of the present invention as antidepressants and related pharmacological properties were determined by studying (1) their ability to affect the efforts of mice to escape from a swim-tank (Porsolt mouse "behavioral despair" test), (2) their ability to potentiate 5-hydroxytryptophan - induced behavioral symptoms in mice in vivo, and (3) their ability to block the uptake of

serotonin, norepinephrine and dopamine by synaptosomal rat brain cells in vitro by the method of Koe, B., Journal of Pharmacology and Experimental Therapeutics, 199 (3), pp. 649-661 (1976).

5       As previously indicated, the trans-isomeric compounds  
of this invention are readily adapted to therapeutic  
use as antidepressant agents. The herein described  
trans-isomers of this invention can be administered as  
antidepressant agents by either the oral or parenteral  
10       routes of administration, without causing any significant  
untoward pharmacological side effects to occur in the  
subject to whom they are administered. In general,  
these antidepressant compounds are normally administered  
in dosages ranging from about 0.3 mg. to about 10 mg.  
15       per kg. of body weight per day, although variations  
will necessarily occur depending upon the conditions of  
the subject being treated and the particular route of  
administration chosen.

In connection with the use of the compounds of this  
20       invention for the treatment of depressed subjects, it is  
to be noted that these compounds may be administered  
either alone or in combination with pharmaceutically  
acceptable carriers by either of the routes previously  
indicated, and that such administration can be carried  
25       out in both single and multiple dosages. More particularly,  
the novel compounds of this invention can be administered  
in a wide variety of different dosage forms, i.e., they  
may be combined with various pharmaceutically-acceptable  
inert carriers in the form of tablets, capsules,  
30       lozenges, troches, hard candies, powders, sprays, aqueous  
suspension, injectable solutions, elixirs, syrups, and  
the like. Such carriers include solid diluents or fillers,

sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage. The compounds of this invention may exist in different polymorphic forms, i.e. different crystalline forms.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of compounds of the invention in sesame or peanut oil or in aqueous propylene glycol or N,N-dimethylformamide may be employed, as well as sterile aqueous solutions of the water-soluble, non-toxic mineral and organic acid addition salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

A typical dry solid pharmaceutical composition is prepared by blending the following materials together in the proportions by weight specified below:

	<u>Trans-(1R)-N-methyl-4-(3,4-</u>	
	<u>dichlorophenyl)-1,2,3,4-</u>	
	<u>tetrahydro-1-naphthalenamine</u>	
	hydrochloride .....	50
	Sodium citrate .....	25
	Alginic acid .....	10
	Polyvinylpyrrolidone .....	10
	Magnesium stearate .....	5

After the dried composition is thoroughly blended, tablets are punched from the resulting mixture, each tablet being of such size that it contains 100 mg. of the active ingredient. Other tablets are also prepared in a similar fashion containing 5, 10, 25 and 50 mg. of the active ingredient, respectively, by using the appropriate amount of the naphthalenamine salt in each case.



Another typical dry solid pharmaceutical composition is prepared by combining the following materials together in the proportions by weight indicated below:

5	<u>Trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine</u>	
	hydrochloride.....	50
	Calcium carbonate.....	20
10	<u>Polyethylene glycol, average molecular weight, 4000.....</u>	30

The dried solid mixture so prepared is then thoroughly agitated so as to obtain a powdered product that is completely uniform in every respect. Soft elastic and hard-filled gelatin capsules containing this pharmaceutical composition are then prepared, employing a sufficient quantity of material in each instance so as to provide each capsule with 50 mg. of the active ingredient.

The following examples illustrate the invention but are not to be construed as limiting the same.

20

EXAMPLE 1

Trans-(1S)(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

A) 3,4-Dichlorobenzophenone

Anhydrous  $AlCl_3$  (219 g., 1.64 moles) was added in portions over a 35 to 40 min. period to a stirred solution of 3,4-dichlorobenzoyl chloride (313.5 g., 1.50 moles) in benzene (1.125 l.) and dichloromethane (75 ml.), with the mixture maintained at 3 to 5°C. during the addition period. The reaction mixture was held at 0 to 5°C. for another hour and then poured into 2.5 l. of ice/water and stirred until the complex had decomposed. The organic and aqueous layers were then separated and the organic layer combined with one ethyl acetate wash of the aqueous layer. The resulting organic

solution was washed twice with water and once with saturated brine solution, dried (anhyd.  $\text{MgSO}_4$ ), treated with decolorizing carbon and evaporated under vacuum to yield an off-white solid, which was

5 recystallized from 400 ml. of hot ethyl acetate-pentane (156.8 g., 41% yield, m.p. 100-102°C., elemental analysis calculated: 62.21% C; 3.21% H; 28.25% Cl; found: 62.17% C; 3.46% H; 28.06% Cl).

10 B) 3-Ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic Acid

A solution of 3,4-dichlorobenzophenone (398 g., 1.58 moles) in *t*-butyl alcohol (1500 ml.) was treated sequentially with potassium *t*-butoxide (169 g., 1.5 moles) and diethyl succinate (402 ml., 2.4 moles).  
15 A mildly exothermic reaction ensued and the initially clear solution set up as a solid mass. The reaction mixture was slowly heated to reflux, at which it became a stirrable white suspension, and then stirred at reflux under nitrogen for about 16 hours. The  
20 reaction mixture was then cooled and poured into 2 liters of ice/water. The resulting mixture was acidified with 10% HCl and extracted with ethyl acetate (3 X 1 l.). The combined ethyl acetate extract was extracted with 1N  $\text{NH}_4\text{OH}$  (3 x 1 l.) and the combined  
25 aqueous basic extract washed with ethyl acetate (2 l.), cooled to 0 to 5°C., acidified slowly to a pH below 1.0 with concentrated HCl and extracted with ethyl acetate (4 X 2 l.). The combined ethyl acetate extract was dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to a  
30 light yellow oil slightly contaminated with diethyl succinate (477 g., 80% yield). An analytical sample was crystallized from petroleum ether (m.p. 128-130°C., elemental analysis calculated: 60.17% C; 4.26% H; 18.70% Cl; found: 60.37% C; 4.35% H; 18.61% Cl).

C) 4-(3,4-Dichlorophenyl)-4-phenylbut-3-enoic Acid

A suspension of 3-ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (227 g., 0.60 mole) in 48% aqueous HBr:glacial acetic acid (1:1, 1.80 l.) was stirred at reflux for 36 hours and then cooled to room temperature. A gum separated from the reaction mixture, which was isolated by decantation of the aqueous layer and then dissolved in ethyl acetate (2 l.). The resulting organic solution was extracted with 10% aqueous  $\text{NH}_4\text{OH}$  (2 X 2 l.). The combined extract was cooled to 0 to 5°C., acidified slowly to a pH below 1.0 with concentrated HCl and extracted with ethyl acetate (4 X 1 l.). The combined ethyl acetate extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to a light brown oil (120 g.), which was crystallized from hexane (91.4 g., 50% yield, m.p. 115-120°C.). An analytical sample of the named compound was recrystallized from hot ethyl acetate-hexane (elemental analysis calculated: 62.58% C; 3.94% H; 23.10% Cl; found: 62.66% C; 4.02% H; 23.22% Cl).

D) 4-(3,4-Dichlorophenyl)-4-phenylbutanoic Acid

A solution of 4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (223 g., 0.73 mole) in ethyl acetate (2 l.) was hydrogenated over 8 grams of 5% Pd/C catalyst at atmospheric pressure and room temperature until hydrogen uptake ceased (about 24 hours). The catalyst was separated by filtration and the filtrate evaporated under vacuum to a light brown oil containing traces of solvent (ca. 100% yield). An analytical sample of the named compound was crystallized from hexane (m.p. 118-120°C., elemental analysis calculated: 62.17% C; 4.57% H; 22.94% Cl; found: 62.08% C; 4.56% H; 23.16% Cl).

E) 4-(3,4-Dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone

A solution of 4-(3,4-dichlorophenyl)-4-phenylbutanoic acid (228 g., 0.74 mole) in toluene (1.2 l.) was treated with thionyl chloride (66 ml., 0.90 mole) and the resulting solution heated at reflux for 75 minutes, with provision made for trapping HCl gas given off from the refluxing reaction solution. The reaction solution was then evaporated under vacuum to about 230 g. of a light brown oil. The oil was dissolved in carbon disulfide (360 ml.) and the resulting solution added to a well stirred suspension of  $AlCl_3$  (1.5 kg., 12.5 moles) in carbon disulfide (1.20 l.), with the mixture held below 8°C. during the addition period, forming a brown mass. After the addition was completed, the reaction mixture was stirred for about 16 hours at room temperature and then slowly poured on ice (vigorous reaction). The resulting suspension was extracted with ethyl acetate (2 X 4 l.). The combined extract was washed with water, washed with saturated aqueous sodium bicarbonate solution, dried and evaporated under vacuum to a residue, which was crystallized from hexane (500 ml.) to yield the named product (104.1 g., 48% yield, m.p. 99-101°C., elemental analysis calculated: 66.00%C; 4.16% H; found: 66.06% C; 4.23% H).

F) Title Compound (Trans-Racemate)

A solution of 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)naphthalenone (13.5 g., 46.3 mmoles) in toluene (190 ml.) was cooled to 0 to 5°C. and treated with 14 ml. (316 mmoles) of methylamine (condensed at 0°C.). Titanium tetrachloride (4.46 g., 23.5 mmoles) was added dropwise to the resulting solution (vigorous reaction), with the reaction mixture stirred at below 10°C. during the addition period. After the addition was completed, the reaction mixture was stirred for 17 hours at room

temperature under nitrogen and then filtered. The solids were washed thoroughly with toluene and the combined filtrates were concentrated under vacuum to remove excess methylamine. Further evaporation to dryness and trituration with hexane yielded the Schiff base (m.p. 145-146°C.).

A suspension of the Schiff base in methanol (75 ml.) was cooled to 14°C. and then treated with sodium borohydride (1.70 g., 45 mmoles, added in portions). The temperature rose to about 28°C. during the addition period. The resulting mixture was stirred for about 90 minutes at about room temperature and then evaporated under vacuum to a gum, which was diluted with water and ether and then filtered. The aqueous layer of the filtrate was extracted twice with ether. The combined organic layers were dried with brine and  $\text{MgSO}_4$  and evaporated under vacuum to an oil, which was chromatographed on silica gel, using an ethyl acetate/hexane/triethylamine (30:20:1) solvent mixture for elution, to separate the cis- and trans-isomers. The trans-isomer was eluted second. The combined eluted fractions containing the trans-isomer were evaporated under vacuum to the crude free base of the named product (4.2 g.), two portions of toluene (100 ml. and 50 ml.) being added to distill away the triethylamine. The free base was then dissolved in ether and converted to the hydrochloride salt by treatment of the ether solution with gaseous hydrogen chloride (trans-racemate; 4.67 g., 33% yield from the naphthalenone, m.p. 214-216°C., elemental analysis calculated: 59.58% C; 5.29% H; 4.09% N; 31.04% Cl; found: 59.59% C; 5.35% H; 4.04% N; 31.01% Cl).

BAD ORIGINAL

EXAMPLE 2

Trans-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

171 mg. (0.50 mmole) of trans-(1S)(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate solution of the trans-racemate free base, which was washed with water, dried ( $\text{MgSO}_4$ ), evaporated under vacuum and treated with a solution of L-(+)-mandelic acid (76 mg., 0.50 mmole) in ethanol. The resulting mixture was evaporated under vacuum to afford a crude material, which was redissolved in ethanol (5 ml.). This ethanol solution was treated with ether (about 15 ml.) to afford a crystalline product (92 mg., m.p. 128-130°C.), which was recrystallized from a mixture of ethanol, ether and hexane (51 mg., m.p. 133-135°C.). This recrystallized product was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate solution of the free base, which was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to a residue. The residue was dissolved in ether and treated with gaseous hydrogen chloride to yield the HCl salt, which was recrystallized from a mixture of methanol and ether [25.7 mg., 15% yield, m.p. 257-258°C.,  $[\alpha]_D^{22} = -39.2^\circ$  ( $\text{CH}_3\text{OH}$ ), elemental analysis calculated: 59.58% C; 5.29% H; 4.09% N; found: 59.31% C; 5.44% H; 4.46% N].

BAD ORIGINAL



EXAMPLE 3Trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

5 The mother liquor from the 92 mg. (1S)-enantiomer crystallization in Example 2 was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate free base solution, which was washed with water, dried ( $\text{MgSO}_4$ ), evaporated under vacuum and treated with a solution of D-(-)-mandelic acid (41 mg., 0.27 mmole) in ethanol (5 ml.) to afford a crystalline product (86 mg., m.p. 132-134.5°C.), which was recrystallized from a mixture of ethanol and ether (52 mg., m.p. 133.5-135°C.). This recrystallized product was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate solution of the free base, which was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to a residue. The residue was dissolved in ether and treated with gaseous hydrogen chloride to yield the HCl salt, which was recrystallized from a mixture of methanol and ether [32 mg., 19% yield from trans-racemate, m.p. 255-257°C.,  $[\alpha]_D^{22} = +41.0$  ( $\text{CH}_3\text{OH}$ )].

EXAMPLES 4-6Trans-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

25 In like manner to that described in Examples 1-3 the named compound was prepared from commercially available 4-chlorobenzophenone and resolved into its enantiomeric forms. Ether, rather than a mixture of methanol and ether, was used as recrystallization solvent, for the HCl salt in Examples 5 and 6.

Example Number	Enantiomer	M.P. (°C.)	$[\alpha]_D^{23}$ (methanol)	Molecular Formula	Elemental Analysis					
					Calculated (%)			Found (%)		
					C	H	N	C	H	N
4	Racemate	247-250	0	$C_{17}H_{18}NCl \cdot HCl$	66.24	6.21	4.55	66.16	6.29	4.53
5	1S	267-270 <sup>d</sup>	-50.5°	$C_{17}H_{18}NCl \cdot HCl$	-	-	-	-	-	-
6	1R	267-270 <sup>d</sup>	+48.2°	$C_{17}H_{18}NCl \cdot HCl$	-	-	-	-	-	-

<sup>d</sup> - decomposed at 270°C.



EXAMPLE 7

Trans-(1S) (1R)-N-methyl-4-(4-fluorophenyl)-1,2,3,4-  
tetrahydro-1-naphthalenamine Hydrochloride

A) 3-Ethoxycarbonyl-4-(4-fluorophenyl)-4-phenyl-  
but-3-enoic Acid

5 A solution of commercially available 4-fluorobenzo-  
phenone (42 g., 0.21 mole), diethyl succinate (43.6 g.,  
0.25 mole) and potassium t-butoxide (23.7 g., 0.21 mole)  
in t-butanol (250 ml.) was stirred at reflux for 6 hours  
10 and then stirred at room temperature for an additional  
16 hours. The reaction mixture was then acidified with  
6N hydrochloric acid (200 ml.), evaporated under vacuum  
to remove the t-butanol and extracted with ether  
(2 X 250 ml.). The combined ether extract was extracted  
15 with 10% aqueous ammonium hydroxide (2 X 350 ml.).  
The combined aqueous extract was washed with ether  
(2 X 200 ml.), re-acidified with 6N hydrochloric acid  
and extracted again with ether (2 X 400 ml.). The  
combined ether extract was dried (MgSO<sub>4</sub>), filtered  
20 and evaporated under vacuum to an oil, which was  
crystallized by dissolution in hexane (100 ml.) followed  
by scratching the flask to initiate crystallization  
(48 g., 70% yield, m.p. 98-99°C., elemental analysis  
calculated: 69.50% C; 5.22% H; 5.78% F; found:  
25 69.34% C; 5.36% H; 6.09% F).

B) 4-(4-Fluorophenyl)-4-phenylbut-3-enoic Acid

3-Ethoxycarbonyl-4-(4-fluorophenyl)-4-phenylbut-  
3-enoic acid (47 g., 0.143 mole) was added to a mixture  
of glacial acetic acid (1000 ml.) and 48% aqueous  
30 hydrobromic acid (500 ml.), and the resulting mixture  
stirred at reflux for 16 hours. The reaction mixture  
was then concentrated under vacuum and the concentrate  
extracted with ether (3 X 500 ml.). The combined

ether extract was extracted with 4% aqueous ammonium hydroxide (5 X 200 ml.). The combined aqueous extract was acidified with 6N hydrochloric acid to a pH of 6.5 and extracted again with ether (3 X 250 ml.). The  
5 combined ether extract was dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to an oil, which solidified on standing. Trituration with hexane gave 15 g. of the named product (47% yield, m.p. 98-100°C., elemental analysis calculated: 74.99% C; 5.11% H; 7.41% F;  
10 found: 74.69% C; 5.40% H; 7.17% F).

C) 4-(4-Fluorophenyl)-4-phenylbutanoic Acid

A solution of 4-(4-fluorophenyl)-4-phenylbut-3-enoic acid (15 g., 0.068 mole) in ethanol (200 ml.) was hydrogenated over 1.0 g. of 10% Pd/C catalyst  
15 for 2 hours at room temperature and 50 psi  $\text{H}_2$ . The reaction mixture was then filtered and evaporated under vacuum to yield a solid, which was recrystallized from an ether/petroleum ether mixture (10.6 g., 70% yield, m.p. 75-75.5°C., elemental analysis calculated:  
20 74.40% C; 5.85% H; 7.36% F; found: 74.62% C; 5.87% H; 7.15% F).

D) 4-(4-Fluorophenyl)-alpha-tetralone

4-(4-Fluorophenyl)-4-phenylbutanoic acid (5 g., 0.019 mole) was treated with anhydrous hydrofluoric acid (20 ml.) and the resulting mixture stirred for  
25 16 hours at room temperature. The reaction mixture was then diluted with water (100 ml.) and extracted with ether (200 ml.). The ether extract was washed with saturated aqueous sodium bicarbonate solution  
30 (50 ml.), washed with water (50 ml.), dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to yield a solid, which was recrystallized from boiling hexane (3.2 g., 69% yield, m.p. 74-75°C., elemental analysis calculated: 79.98% C; 5.45% H; found: 80.00% C; 5.66% H).

E) Title Compound (Trans-Racemate)

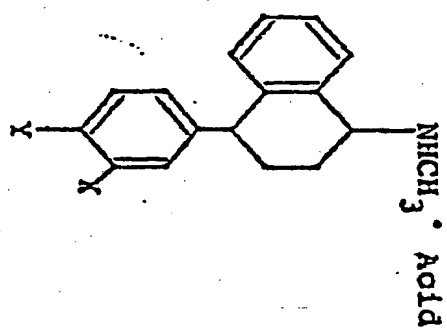
A solution of 4-(4-fluorophenyl)-alpha-tetralone (3.0 g., 0.012 mole) in toluene (50 ml.) was cooled to 10°C. and treated at that temperature with methylamine (2.0 g., 0.064 mole) and then titanium tetrachloride (dropwise addition, 1.73 g., 0.009 mole). The reaction mixture was then stirred for 16 hours at room temperature, filtered and evaporated under vacuum to yield a crude 1-imine solid. The crude imine was dissolved in methanol (50 ml.), the methanol solution treated with sodium borohydride (1.0 g., 0.026 mole) and the resulting mixture stirred for 16 hours at room temperature. The reaction mixture was then evaporated under vacuum to an oily solid, which was dissolved in ether (200 ml.). The ether solution was washed with water (3 X 50 ml.), dried (MgSO<sub>4</sub>), filtered and evaporated under vacuum to an oil. The oil was chromatographed on silica gel, using an ethyl acetate/hexane/diethylamine (16/16/0.3) solvent mixture for elution, to separate the cis- and trans-isomers. The trans-isomer was eluted second and converted to its hydrochloride salt by treating the eluted fractions with gaseous hydrogen chloride. This hydrochloride salt was recrystallized from a mixture of methanol and ether to give 240 mg. of the title compound (trans-racemate, 7% yield, m.p. 210-211°C., elemental analysis calculated: 69.98% C; 6.56% H; 4.80% N; found: 69.84% C; 6.49% H; 4.81% N).

EXAMPLES 8-10

In like manner to that described in Example 7, the following compounds (trans-racemates) were prepared from the appropriate substituted benzophenones. In the case of Example 9, the 1-imine solid was prepared as in step 7E, but the following procedure was used instead of the remainder of step 7E:

E) Trans-(1S)(1R)-N-methyl-4-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Maleate from 1-Imine

A 1 g. sample of elemental zinc was activated by treatment with 1N HCl (10 ml.) followed by washing with ethanol and acetone. The activated zinc was then added to a solution of N-methyl-4-(3-trifluoromethyl-phenyl)-3,4-dihydro-1-(2H)naphthalenimine (0.90 g., 2.96 mmoles) in glacial acetic acid (10 ml.) and the resulting mixture stirred for 5 hours in a 70°C. bath. The reaction mixture was then cooled, filtered to remove the zinc and evaporated under vacuum to an oil. This oil was combined with an oil produced from a second run (as per Example 7E) starting with 16.0 mmoles of 1-imine and then chromatographed on silica gel, using an ethyl acetate/hexane/diethylamine (30/20/1) solvent mixture for elution, to separate the cis- and trans-isomers. The title compound was isolated by treatment of the trans-isomer free base in solution with maleic acid (493 mg., 7% yield).



## Elemental Analysis

Example #	X	Y	M.P. (°C)	Molecular Formula	Calculated (%)						Found (%)					
					C	H	N	F			C	H	N	F		
8	H	CF <sub>3</sub>	260-261	C <sub>18</sub> H <sub>18</sub> NF <sub>3</sub> ·HCl	63.24	5.60	4.10	16.67			62.93	5.64	4.18	16.95		
9	CF <sub>3</sub>	H	143-145	C <sub>18</sub> H <sub>18</sub> NF <sub>3</sub> ·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	62.70	5.26	3.32	-			62.41	5.31	3.42	-		
10	CF <sub>3</sub>	Cl	218-219	C <sub>18</sub> H <sub>17</sub> NF <sub>3</sub> Cl·HCl	57.46	4.82	3.72	-			57.08	4.62	3.68	-		

The combined ether extract was washed with saturated aqueous sodium bicarbonate solution (3 X 100 ml.), washed with water (100 ml.), dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to yield the desired tetralone (2.2 g., 67% yield, m.p. 106-107°C.).

#### EXAMPLE 12

##### Trans-(1S)(1R)-N-methyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

In like manner to that described in Example 7 A, B and E and Example 11 D, the named compound (trans-racemate) was prepared from commercially available 4-bromobenzophenone (m.p. 288-289°C., elemental analysis calculated: 57.89% C; 5.43% H; 3.97% N; found: 57.69% C; 5.11% H; 4.00% N). In place of step 7C, the following procedure was employed:

##### C) 4-(4-Bromophenyl)-4-phenylbutanoic Acid

A solution of 4-(4-bromophenyl)-4-phenylbut-3-enoic acid (5.0 g., 0.0157 mole) in glacial acetic acid (50 ml.) was treated with 56.9% aqueous hydriodic acid (22.5 ml.) and red phosphorus (4.5 g.) and the resulting mixture stirred at reflux for 16 hours. The reaction mixture was then cooled to room temperature, diluted with saturated aqueous sodium chloride solution (250 ml.) and extracted with methylene chloride (250 ml.). The extract was washed with saturated aqueous sodium chloride solution (2 X 100 ml.), dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to the desired butanoic acid derivative, which was used in the next step without further purification (5 g., oil, ca. 99% yield).

#### EXAMPLE 13

##### Trans-(1S)(1R)-N-methyl-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

The appropriate substituted benzophenone starting materials for Examples 8-10 were prepared as shown below for 4-trifluoromethyl-benzophenone:

A) 4-Trifluoromethyl-benzophenone

5        2.91M phenyl magnesium bromide (90 ml., 0.26 mole) was added dropwise over a 45 minute period to a solution of 4-trifluoromethyl-benzonitrile (40 g., 0.23 mole) in ether (400 ml.) and the resulting mixture stirred for 3 days at room temperature. The reaction mixture was then cooled  
10        in an ice-water bath, treated slowly with saturated aqueous ammonium chloride solution (150 ml.) and then treated with 1N HCl (100 ml.). The ether layer was removed and the aqueous layer extracted with ether (2 X 200 ml.). The three ether layers were combined,  
15        washed with 1N HCl (2 X 100 ml.), washed with water (2 X 200 ml.), dried (MgSO<sub>4</sub>), treated with activated carbon, filtered, and evaporated under vacuum to yield a solid, which was then crystallized from 200 ml. of hot hexane (36 g., 62% yield, m.p. 107-108°C.). An  
20        analytical sample of the named compound was recrystallized from hexane (m.p. 116-118°C.).

EXAMPLE 11

Trans-(1S) (1R)-N-methyl-4-(4-chlorophenyl)-7-chloro-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

25        In like manner to that described in Example 7 A-C and E, the named compound (trans-racemate) was prepared from commercially available 4,4'-dichlorobenzophenone (m.p. 295 - 296°C., elemental analysis calculated: 59.58% C; 5.29% H; 4.09% N; found: 59.35% C; 5.12% H;  
30        4.13% N). In place of step 7D, the following procedure was employed:

D) 4-(4-Chlorophenyl)-7-chloro-alpha-tetralone

35        4,4-Di(4-chlorophenyl)butanoic acid (3.5 g., 0.0113 mole) was treated with polyphosphoric acid (80 g.) and the resulting mixture treated for 4 hours at 120°C. The reaction mixture was then poured onto crushed ice and the product extracted with ether (3 X 150 ml.).

A) 1-Hydroxy-1-(4-methoxyphenyl)tetralin

A solution of 4-bromo-anisole (25 g., 0.134 mole) in tetrahydrofuran (100 ml.) was prepared. Magnesium (3.24 g., 0.123 mole) was treated with a small portion of this solution and heated until a reaction started (55°C.). The remainder of the solution was added dropwise and, after the addition was complete, the mixture was stirred for 2 hours at 55°C. The reaction mixture was then cooled to room temperature and a solution of 1-tetralone (17.92 g., 0.123 mole) in tetrahydrofuran (100 ml.) slowly added. Stirring was continued at room temperature for 16 hours after the addition was complete. Ether (200 ml.) and water (200 ml.) were then added to the reaction mixture, followed by 10% aqueous ammonium chloride solution (100 ml.). The ether layer was separated, dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to an oil, which was used without further purification in the next step (18 g., 58% yield).

B) 1-(4-Methoxyphenyl)-3,4-dihydro-naphthalene

A solution of 1-hydroxy-1-(4-methoxyphenyl)-tetralin (18 g., 0.071 mole) in toluene (250 ml.) was treated with para-toluenesulfonic acid (5 mg.) and the resulting solution stirred at reflux for 16 hours, with complete water removal accomplished by means of a Dean-Stark trap. The reaction mixture was then cooled to room temperature, washed sequentially with 10% aqueous sodium bicarbonate solution (100 ml.), water (100 ml.) and saturated aqueous sodium chloride solution (100 ml.), dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to an oil, which was purified by silica gel chromatography (elution with a hexane-toluene gradient) to give 12 g. of the named compound (67% yield, oil).



C) 1-(4-Methoxyphenyl)tetralin

1-(4-Methoxyphenyl)-3,4-dihydro-naphthalene (12 g., 0.051 mole) was added to a mixture of 10% Pd on carbon catalyst (1.0 g.) and ethanol (250 ml.) and hydrogenated for 4 hours at room temperature and 50 psi of H<sub>2</sub>. The reaction mixture was then filtered and evaporated under vacuum to an oil, which was used in the next step without further purification (11.2 g., 92.5% yield).

D) 4-Hydroxy-4-(4-methoxyphenyl)-1-tetralone

1-(4-Methoxyphenyl)tetralin (11.2 g., 0.047 mole) was dissolved in a solution of potassium permanganate (36.7 g.) in acetone (1.6 l.) and water (33 ml.), and the resulting solution stirred at reflux for 16 hours. The reaction mixture was then filtered, treated again with potassium permanganate (36.7 g.) and stirred at reflux for another 16 hours. This process was continued until a total of three reaction cycles had been run. After the third 16 hour reaction period, the reaction mixture was filtered, treated with activated charcoal, filtered and evaporated under vacuum to a residue. The residue was taken up in ethyl acetate (200 ml.) and the ethyl acetate solution washed with saturated aqueous sodium chloride solution (200 ml.), filtered, washed again with saturated aqueous sodium chloride solution (200 ml.), dried (MgSO<sub>4</sub>), filtered and evaporated under vacuum to yield a solid, which was recrystallized from a mixture of ethyl acetate and hexane (3.9 g., 23% yield).

E) N-methyl-4-hydroxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of 4-hydroxy-4-(4-methoxyphenyl)-1-tetralone (3.9 g., 0.0138 mole) in tetrahydrofuran

(40 ml.) was cooled to 0°C. and the cooled solution treated with methylamine (5 ml.) followed by dropwise addition of titanium tetrachloride (1 ml.). The resulting mixture was stirred for 16 hours at room temperature, filtered and evaporated under vacuum to an oil, which was dissolved in absolute ethanol (20 ml.). The ethanol solution was treated with sodium borohydride (1.0 g., 0.0264 mole) and stirred for 1 hour at room temperature. The reaction mixture was then evaporated under vacuum to a residue and the residue taken up in ethyl acetate (125 ml.). The ethyl acetate solution was washed with water (125 ml.), washed with saturated aqueous sodium chloride solution (125 ml.), dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to an oil, which was used in the next step without further purification (3.4 g., 83% yield, mixture of cis- and trans-isomers).

F) N-methyl-4-(4-methoxyphenyl)-1,2-dihydro-1-naphthalenamine Hydrochloride

A solution of N-methyl-4-hydroxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (1.9 g., 0.0069 mole, mixture of cis- and trans-isomers) in ether (50 ml.) was treated with gaseous hydrogen chloride. The solution was then evaporated under vacuum to yield a white solid, which was recrystallized from ethyl acetate (1.5 g., 72% yield, m.p. 221-222°C.).

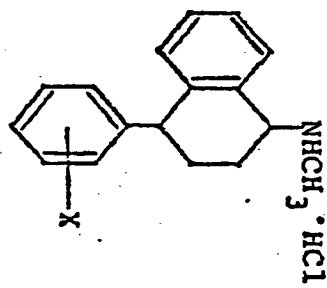
G) Title Compound (Cis-Racemate)

N-methyl-4-(4-methoxyphenyl)-1,2-dihydro-1-naphthalenamine hydrochloride (1.5 g., 0.0049 mole) was mixed with ethanol (30 ml.) and 10% palladium on carbon catalyst (250 mg.) and hydrogenated for 4 hours at room temperature and 45 psi of  $\text{H}_2$ . The reaction mixture was then filtered and evaporated under vacuum to

5 a residue. The residue was chromatographed on silica gel (elution with ethyl acetate containing 1% ammonium hydroxide) to separate the cis- and trans-isomers. The trans-isomer was converted to the hydrochloride salt, which was recrystallized from a mixture of chloroform and ether (461 mg., 31% yield, m.p. 230-233°C., elemental analysis calculated: 71.15% C; 7.29% H; 4.61% N; found: 70.60% C; 7.45% H; 4.51% N).

EXAMPLES 14-15

10 In like manner to that described in Example 13 the following compounds (trans-racemates) were prepared from 2-bromo-anisole and 3-bromo-anisole:



Example Number	X	M.P. (°C.)	Molecular Formula	Elemental Analysis					
				Calculated(%)			Found(%)		
				C	H	N	C	H	N
14	2-OCH <sub>3</sub>	201-203	C <sub>18</sub> H <sub>21</sub> ON·HCl·1/3 H <sub>2</sub> O	69.99	7.37	4.53	70.21	7.05	4.53
15	3-OCH <sub>3</sub>	166-169	C <sub>18</sub> H <sub>21</sub> ON·HCl	71.14	7.29	4.63	70.84	7.20	4.84

EXAMPLE 16

Trans-(1S) (1R)-N-methyl-4-(2,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

5 In like manner to that described in Example 11, the named compound (trans-racemate, m.p. 195-196°C.) was prepared from 2,4-dichlorobenzophenone.

EXAMPLE 17

Trans-(1S) (1R)-N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

10 In like manner to that described in Example 13 A, D to F, the named compound (trans-racemate) was prepared from commercially available 4-bromochlorobenzene and 6-methoxy-1-tetralone. Steps B and C of Example 13 were omitted. The following procedure was employed in place  
15 of step 13G:

G) Title Compound (Trans-Racemate)

A solution of N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2-dihydro-1-naphthalenamine hydrochloride (5.1 g., 0.015 mole) in trifluoroacetic acid (24 g.)  
20 was added to a solution of triethylsilane (1.76 g., 0.015 mole) in trifluoroacetic acid (10 g.), and the resulting mixture stirred for 2 hrs. at 60°C. The reaction mixture was then cooled to room temperature and treated with water (200 ml.) and ether (200 ml.). The  
25 ether layer was withdrawn and the aqueous layer then extracted with ethyl acetate (2 X 100 ml.). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (3 X 100 ml.), washed with water (200 ml.), dried (MgSO<sub>4</sub>), filtered and evaporated under  
30 vacuum to an oil, which was crystallized from 50 ml. ether (cis-racemate, m.p. 275-276°C., 2.0g.).

The mother liquor from the cis-racemate crystallization was then evaporated under vacuum to an oil, which was chromatographed on silica gel. (elution with ethyl acetate containing 1% ammonium hydroxide). Fractions containing the trans-isomer were evaporated under vacuum to an oil, which was dissolved in chloroform (50 ml.) and converted to the hydrochloride salt. The HCl salt was then crystallized from ethyl acetate (20 mg., 0.4% yield, m.p. 217-219°C., 1/4 mole water per mole named compound, elemental analysis calculated: 63.07% C; 6.32% H; 4.09% N; found: 63.08% C; 6.22% H; 4.18% N).

#### EXAMPLE 18

Trans-(1S)(1R)-N,N-dimethyl-4-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Maleate

In like manner to that described in Example 7 A-D the named compound (trans-racemate) was prepared from 3-trifluoromethyl-benzophenone (m.p. 99.5-101°C., 1/2 mole H<sub>2</sub>O per mole named compound, elemental analysis calculated: 62.16% C; 5.67% H; 3.15% N; found: 62.34% C; 5.42% H; 3.12% N). In place of step 7E, the following procedure was employed:

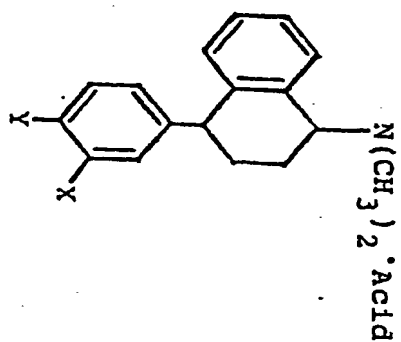
#### E) Title Compound (Trans-Racemate)

A solution of 4-(3-trifluoromethylphenyl)- $\alpha$ -tetralone (3.0 g., 0.010 mole) in toluene (50 ml.) was treated, under cooling in an ice bath, with dimethylamine (3 ml., 0.045 mole) followed by titanium tetrachloride (dropwise addition, 1.2 ml., 0.011 mole). The reaction mixture was then stirred for 16 hours at room temperature, filtered and evaporated under vacuum to yield a crude 3,4-dihydro-1-dimethylanino-4-aryl-naphthalene solid. The crude enamine was added to a mixture of glacial acetic acid (5 ml.), sodium borohydride (1.3 g., 0.034 mole) and tetrahydrofuran.

(50 ml.), and the resulting mixture stirred for 3 hours at room temperature. The reaction mixture was then evaporated under vacuum to an oily solid, which was treated with water (100 ml.) and extracted with ether (200 ml.). The ether extract was dried ( $\text{MgSO}_4$ ), filtered and evaporated under vacuum to an oil. The oil was chromatographed on silica gel, using a 0.5% diethylamine/hexane solvent mixture for elution, to separate the cis- and trans-isomers. The trans-isomer was eluted second. The eluted fractions were evaporated under vacuum, dissolved several times in methanol and evaporated again under vacuum to an oil (204 mg.). The oil was dissolved in methanol and the methanol solution treated with maleic acid (74 mg., 0.00064 mole), heated to dissolve the acid and then evaporated under vacuum to yield the named compound, which was then crystallized from a mixture of ether and petroleum ether (190 mg., 4% yield, m.p. 99.5-101°C.).

#### EXAMPLES 19-20a

In like manner to that described in Example 18 the following compounds (trans-racemates) were prepared from the appropriate substituted benzophenones:



### Elemental Analysis

Example Number	X	Y	M.P. (°C.)	Molecular Formula	Calculated(%)			Found(%)		
					C	H	N	C	H	N
19	H	CF <sub>3</sub>	120-122	C <sub>19</sub> H <sub>20</sub> NF <sub>3</sub> ·1/4H <sub>2</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	62.79	5.62	3.18	62.70	5.77	3.20
20	H	Cl	140-141	C <sub>18</sub> H <sub>20</sub> NCl·1/2H <sub>2</sub> O·HCl	65.26	6.69	4.23	65.37	6.82	4.27
20a	Cl	Cl	229-231 <sup>d</sup>	C <sub>18</sub> H <sub>19</sub> NCl <sub>2</sub> ·1/4H <sub>2</sub> O·HCl	59.85	5.72	3.88	59.88	5.41	3.86

<sup>d</sup> - decomposes



EXAMPLES 20b-20c

In like manner to that described in Example 13 the following compounds (trans-racemates) and their acid addition salts may be prepared from 2-fluoro-4-bromo-anisole and 2-fluoro-5-bromo-anisole, respectively:

<u>Example</u>	<u>Compound</u>
20b	<u>Trans</u> -(1S)(1R)-N-methyl-4-(3-fluoro-4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
20c	<u>Trans</u> -(1S)(1R)-N-methyl-4-(3-methoxy-4-fluorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

EXAMPLE 21

Blockade of Synaptosomal Uptake of Serotonin (5HT),  
Dopamine (DA) and Norepinephrine (NE) In Vitro by  
Trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-  
tetrahydro-1-naphthalenamine Hydrochloride

Sprague-Dawley CD male rats weighing 180-220 g.  
(Charles River Laboratories, Inc.; Wilmington, Mass.)  
were used in this procedure. A crude synaptosomal  
fraction of rat corpus striatum (for 5HT and DA uptake)  
or hypothalamus (for NE uptake) tissue was prepared by  
homogenizing tissue (25 ml./g. wet) in ice-cold 0.32M  
sucrose containing 1 mg./ml. glucose, 0.0001M EDTA  
and tris(hydroxymethyl)aminomethane to pH 7.4.  
The homogenate was centrifuged at 1000 X g for 10 min.  
at 0-4°C., the pellet discarded and the supernatant  
centrifuged at 17,000 X g for 20 min. at 0-4°C. The  
resulting pellet was resuspended in the ice-cold 0.32M  
sucrose pH 7.4 solution at 10 ml./g. original tissue  
(wet) for corpus striatum and 5 ml./g. original tissue  
(wet) for hypothalamus. An incubation buffer was  
prepared: 25mM tris(hydroxymethyl)aminomethane, adjusted  
to pH 7.4 with HCl, containing 124mM NaCl, 4.5mM KCl,  
1.2mM  $\text{KH}_2\text{PO}_4$ , 1.3mM  $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ , 0.001mM ascorbic acid,  
0.0125mM nialamide hydrochloride and 2.8mM  $\text{CaCl}_2$ .  
Duplicate 0.1 ml. aliquots of the tissue suspension  
were incubated for 10 min. at 37°C. with 0.02 ml. of a  
solution containing a known quantity of the named test  
compound and 1.0 ml. of the incubation buffer containing  
additionally 1 mg./ml. glucose and 0.0001mM labeled  
monoamine ( $^{14}\text{C}$ -5HT,  $^{14}\text{C}$ -DA or  $^3\text{H}$ -NE). After incubation,  
the mixtures were filtered through 0.45 micron Millipore  
filters and the filters washed with the incubation  
buffer. The filtered materials were dissolved in 1.0 ml.  
of 2-methoxyethanol and analyzed for radioactivity by

liquid scintillation counting (uptake at 0°C. taken as radiation blank). Uptake was calculated as picomoles 5HT, DA or NE per mg. protein (protein was determined by measurement with Folin phenol reagent). The  $IC_{50}$ , the concentration of named test compound (expressed as micromoles per liter in ca. 1 ml. incubation mixture) inhibiting uptake by 50% from that calculated for test compound-free control aliquots, was estimated from plots of % uptake inhibition vs. concentration on semilog paper to be 0.039 micromolar for 5HT, 0.044 micromolar for DA and 0.017 micromolar for NE.

#### EXAMPLES 22-40c

In like manner to that described in Example 21 the blockade of synaptosomal uptake was determined in vitro for the compounds listed below.

Example Number	Compound Prepared in Example Number	$IC_{50}$ (micromoles/liter) <sup>a</sup>		
		Corpus Striatum	Hypothalamus	
		5HT	DA	NE
22	1	0.050	0.057	0.022
23	2	0.47	0.27	0.044
24	4	0.13	0.11	0.030
25	6	0.084	0.052	0.019
26	5	3.5	1.4	0.46
27	7	0.58	0.22	0.027
28	8	0.43	4.4	0.69
29	9	0.39	2.6	0.26
30	10	1.4	7.3	0.89
31	11	0.16	0.045	0.028
32	12	0.090	0.080	0.029
33	13	0.38	0.40	0.15
34	14	4.5	5.7	0.48
35	15	0.34	0.53	0.060
36	16	1.05	6.1	0.97
37	17	0.15	0.042	0.017
38	18	0.22	6.1	1.4
39	19	0.49	9.8	4.7
40	20	0.12	0.38	0.13
40a	20a	0.04	0.17	0.04
40b	Comparative <sup>b</sup> Example I	1.5	0.21	0.037
40c	Comparative <sup>c</sup> Example II	0.46	0.84	0.14

a - H = high activity, M = moderate activity, L = low activity. For 5HT and DA uptake blockade: H,  $IC_{50}$  less than 1 micromolar; M,  $IC_{50}$  1-5 micromolar; L,  $IC_{50}$  greater than 5 micromolar. For NE uptake blockade:  
5 H,  $IC_{50}$  less than 0.1 micromolar; M,  $IC_{50}$  0.1-0.5 micromolar; L,  $IC_{50}$  greater than 0.5 micromolar.

b - Trans-(1S)(1R)-N-methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (U.S. Patent 4,029,731).

10 c - Trans-(1S)(1R)-N,N-dimethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (U.S. Patent 4,029,731).

EXAMPLE 41

Reduction of Behavioral Despair In Vivo (Modified Porsolt Method) by Trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride

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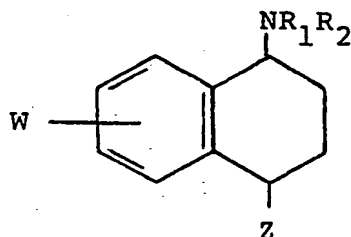
5        A modification of the procedure described by Porsolt et al., Arch. Int. Pharmacodyn., 229, pp. 327-336 (1977) was used. A number of Swiss-Webster CD male mice weighing 25-30 g. (Charles River Laboratories, Inc.; Wilmington, Mass.) were housed under standard laboratory conditions  
10       for at least one week prior to experimentation. Groups of 10 mice were then injected subcutaneously with either a given dosage of the named test compound or vehicle (5% Emulphor: 5% ethanol: 90% normal saline). One hour later the mice were placed individually in 1 liter beakers containing 7 cm. of 25°C. water. Beginning at 2 min. after  
15       immersion, each mouse was observed every 30 sec. for the presence of immobility, characterized as floating motionless in the water. A total of ten observations were made, each being scored as "0 = animal moving, swimming, attempting to escape" or "1 = animal immobile".  
20       The number of positive observations for each mouse was then totaled and a mean immobility score calculated for the group of ten. For dose-response analysis, this data was converted to % MPE (maximum possible effect) values,  
25       defined as:

$$\% \text{ MPE} = \frac{\text{Control mean} - \text{Test mean}}{\text{Control mean}} \times 100\%$$

-1-

CLAIMS

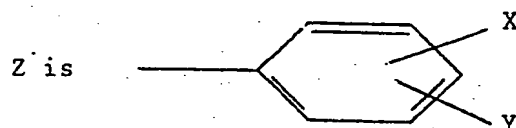
1. A trans-isomeric base of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

$R_1$  is hydrogen or normal alkyl of from 1 to 3 carbon atoms,

$R_2$  is normal alkyl of from 1 to 3 carbon atoms,



X and Y are each hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms or cyano, with at least one of X and Y being other than hydrogen, and

W is hydrogen, fluoro, chloro, bromo, trifluoromethyl or alkoxy of from 1 to 3 atoms.

2. A compound of claim 1 wherein said compound is either the (1R)-enantiomer or the racemic mixture of the (1R)-enantiomer with the corresponding (1S)-enantiomer.

3. A compound of claim 2 wherein  $R_1$  is hydrogen or methyl,  $R_2$  is methyl and Z is 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-bromophenyl or 4-bromophenyl.

4. A compound of claim 3 wherein W is hydrogen.

5. A compound of claim 3 wherein  $R_1$  is hydrogen.

6. A compound of claim 2 wherein  $R_1$  is methyl,  $R_2$  is methyl, W is hydrogen and Z is 3-trifluoromethylphenyl or 4-trifluoromethylphenyl.

7. A compound of claim 1 wherein said compound is:

Trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N-methyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N,N-dimethyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N,N-dimethyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N,N-dimethyl-4-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;

Trans-N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine; or

Trans-N-methyl-4-(4-chlorophenyl)-7-chloro-1,2,3,4-tetrahydro-1-naphthalenamine;

in either the (1R)-enantiomeric or (1S) (1R) racemic forms, and their pharmaceutically acceptable acid addition salts.

8. A compound of claim 1 wherein said compound is:

Trans-(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine and its pharmaceutically acceptable acid addition salts.

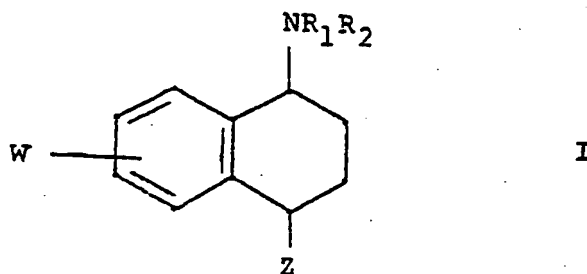
9. A compound of claim 1 wherein said compound is:

Trans-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine and its pharmaceutically acceptable acid addition salts.

10. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 in an amount effective in combatting mental depression as the essential active ingredient together with a pharmaceutically acceptable diluent or carrier.

CLAIMS FOR AUSTRIA

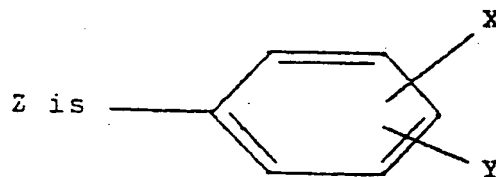
1. A process for preparing a trans-isomeric base of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

$R_1$  is hydrogen or normal alkyl of from 1 to 3 carbon atoms,

$R_2$  is normal alkyl of from 1 to 3 carbon atoms,

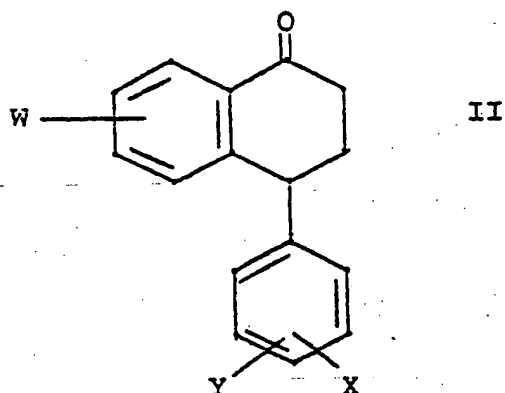


X and Y are each hydrogen, fluoro, chloro, bromo, trifluoromethyl or cyano, with at least one of X and Y being other than hydrogen, and

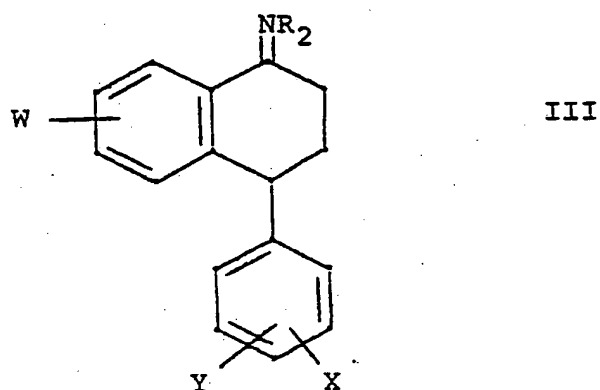
W is hydrogen, fluoro, chloro, bromo, trifluoromethyl or alkoxy of from 1 to 3 carbon atoms, which process comprises the steps of

(a) condensing a compound of the formula

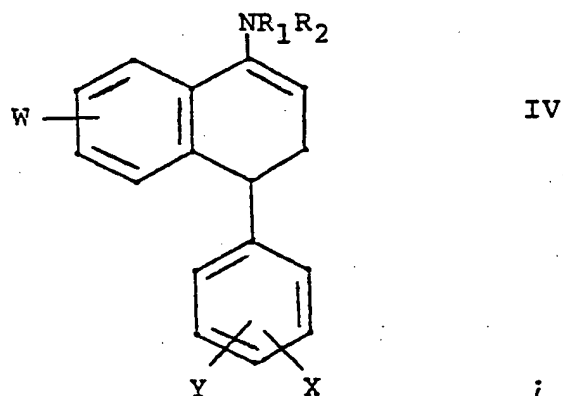




with an amine of the formula  $\text{HNR}_1\text{R}_2$  in the presence of an acid catalyst to obtain, when  $\text{R}_1$  is hydrogen, a compound of the formula



or, when  $\text{R}_1$  is normal alkyl, a compound of the formula



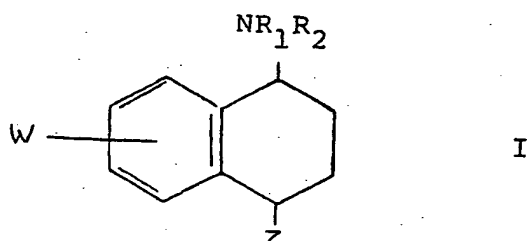
(b) reducing the resulting compound of formula III or IV to obtain a mixture of cis- and trans-isomeric bases of formula I;

(c) separating a trans-isomeric base of formula I from said mixture resulting from step (b); and

(d) if desired, converting the trans-isomeric base of formula I resulting from step (c) to a pharmaceutically acceptable acid addition salt thereof.

2. A process of claim 1 wherein  $R_1$  is hydrogen or methyl,  $R_2$  is methyl and Z is 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-bromophenyl, or 4-bromophenyl.

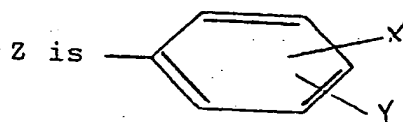
3. A process for preparing a trans-isomeric base of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

$R_1$  is hydrogen or normal alkyl of from 1 to 3 carbon atoms,

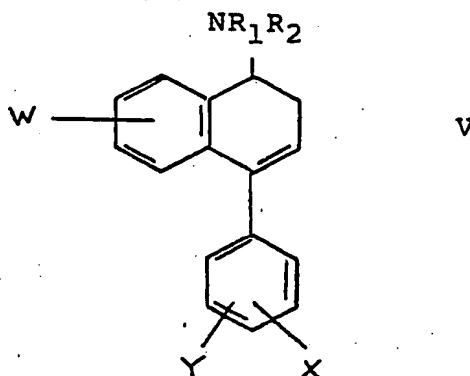
$R_2$  is normal alkyl of from 1 to 3 carbon atoms,



X and Y are each hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms or cyano, with at least one of X and Y being other than hydrogen, and

W is hydrogen, fluoro, chloro, bromo, trifluoromethyl or alkoxy of from 1 to 3 carbon atoms, which process comprises the steps of

(a) hydrogenating a compound of the formula



to obtain a mixture of cis- and trans-isomeric bases of formula I;

(b) separating a trans-isomeric base of formula I from said mixture resulting from step (a); and

(c) if desired, converting the trans-isomeric base of formula I resulting from step (b) to a pharmaceutically acceptable acid addition salt thereof.

4. A process of claim 2 wherein  $R_1$  is hydrogen or methyl,  $R_2$  is methyl and Z is 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-bromophenyl, or 4-bromophenyl.

5. A process as claimed in claim 2 or claim 4 wherein W is hydrogen,

$R_1$  is methyl,  $R_2$  is methyl, and Z is 3-trifluoromethylphenyl or 4-trifluoromethylphenyl.

6. A process as claimed in claim 2 or claim 4 wherein  $R_1$  is hydrogen, W is hydrogen and Z is 3,4-dichlorophenyl.

7. A process as claimed in claim 2 or 4 wherein  $R_1$  is methyl, W is hydrogen and Z is 3,4-dichlorophenyl.

0028901

European Patent  
Office

## EUROPEAN SEARCH REPORT

Application number

EP 80 30 3810.8

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	DE - A - 2 348 577 (PFIZER) * claims 1 and 8 to 12 * --	1,10	C 07 C 87/457 C 07 C 93/12 C 07 C 93/14
A,D	US - A - 4 029 731 (R. SARGES) * claim 1 *	1,10	C 07 C 85/26 A 61 K 31/135
A,D	US - A - 4 045 488 (R. SARGES) * claim 1 *	1,10	
			TECHNICAL FIELDS SEARCHED (Int. Cl.3)
A	JOURNAL OF ORGANIC CHEMISTRY, Vol 40, No. 9, 1975 Columbus R. SARGES "Synthesis of Phenyl-Substituted 1-Aminotetralines" * page 1217, formulas 19 and 20 * --	1	A 61 K 31/135 C 07 C 85/26 C 07 C 87/457 C 07 C 93/12 C 07 C 93/14
A	Chemical Abstracts vol. 82, no. 23, 1973 Columbus, Ohio, USA R. SARGES et al. "Blockade of heart tritium-labeled-norepinephrine uptake by 4-phenyl-1-aminotetralins. Implications for the active conformation of imipraminelike drugs" page 10, column 2 and page 11, column 1, abstract no. 149170f & J. Pharmacol. Exp. Ther., vol. 191, no. 3, 1974, pages 393 to 402 ----	1,2,10	
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
X The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
Berlin	16-02-1981	KNAACK	

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